T*oxicology*
E*xcellence for*
R*isk*
A*ssessment*

TERA is a non-profit 501(c)(3) corporation dedicated to the best use of toxicity data for risk assessment.

Perchlorate EPA Document Development and Peer Review

Joan Dollarhide, M.S., MSTC, J.D.

Toxicology Excellence for Risk Assessment (*TERA*)

Purpose

- Provide an overview of EPA's external peer review of the perchlorate risk assessment
- Summarize the panel conclusions and provide context for the discussions of the ongoing round of perchlorate studies that are the focus of this meeting

History of Perchlorate RfD

- EPA Superfund provisional Reference Dose 1992, revised 1995
- *TERA* RfD and expert peer review 1997 - data are inadequate, suggest specific studies
- 1997-1999 Air Force and PSG complete recommended studies
- 1999 EPA draft document and RfD based on new data peer reviewed

RfD Definition

- Reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfDs are based on non-carcinogenic effects and are usually calculated by applying uncertainty factors to a NOAEL or LOAEL. Expressed as mg/kg-day.

EPA Provisional RfD 1992/5

- EPA Superfund Technical Support Center
- Based on acute study in patients with Graves' Disease (Stanbury and Wyngaarden, 1952)
- NOAEL 0.14 mg/kg-day - release of iodine in thyroid followed by incomplete inhibition of iodine uptake
- Uncertainty factor 300 to 1000
- Results in ground water cleanup guidance level of 4 to 18 ppb

TERA Expert Peer Review 1997

- Additional literature search to answer outstanding questions from EPA provisional RfD
- Considered Caldwell study, not available to EPA
- Developed a RfD based on similar database as EPA's RfD, peer reviewed in 1997

TERA Expert Peer Review 1997

Conclusion:

Perchlorate database insufficient

to develop any RfD

Major unanswered questions:

- shape of dose-response curve in humans
- effects from long-term exposure
- possibility of effects in organs/systems other than thyroid

Recommended Studies

- Neurobehavioral developmental
- 90-day subchronic oral bioassay
- Segment II developmental
- Two-generation reproductive
- ADME
- Genotoxicity assays
- Immunotoxicity studies
- Mechanism studies

EPA Perchlorate Document

- National Center for Environmental Assessment (NCEA)
- Evaluated new studies and entire database
- Harmonization of noncancer and cancer risk assessment using Mode of Action (MOA) analysis
- Proposed RfD of 0.0009 mkd, based on thyroid histopathology in rat pups PND5 in neurodevelopmental study (Argus 1998)
- Screening ecological risk assessment

External Peer Review

- External peer review of EPA draft document and the new studies
- Peer review organized by outside contractor
- February 10-11, 1999
- San Bernardino, CA

Peer Review: a documented critical review of a specific Agency major scientific and/or technical work product.

Perchlorate Review:

- public meeting
- independent panel
- observer comments
- report
- stakeholder involvement

Selection of Peer Review Panel

- Panel of experts selected by RTI
- EPA identified preferred expertise
- RTI reviewed credentials and selected panel from pool of scientists nominated by stakeholders
- Experts had no conflicts of interest

Peer Reviewers

- Dr. Joseph Haseman, biostatistics
- Dr. Susan P. Porterfield, thyroid function and toxicology
- Dr. Charles H. Emerson, medical endocrinology
- Dr. R. Thomas Zoeller, neurotoxicology
- Dr. Rochelle W. Tyl, developmental/reproductive toxicology
- Dr. Kimber White, immunotoxicology
- Dr. David Brusick, genetic toxicology
- Dr. Rick Cardwell, ecotoxicology
- Dr. Curtis Klaaseen, general toxicology
- Dr. Mel Andersen, risk assessment and PBPK modeling

Stakeholder Involvement

- Several stakeholder meetings held
- Stakeholders nominated candidate peer reviewers
- Observers given time to present to peer review panel.

Charge to Peer Review Panel

- **The panel was asked to review the assessment document and toxicity database in four areas:**
  1. Studies initiated since May 1997
  2. Review of Toxicological Document
  3. Hazard Characterization
  4. Further Testing Needs

1. Review of Studies Initiated Since May 1997

Strengths and weaknesses of experimental design

- Limitations which would decrease relevance of findings
- Statistical methods
- Presentation of results adequate?
- Appropriate for hazard characterization purposes?
- For studies not yet complete (e.g., 2-gen study), possible to derive meaningful conclusions at this time?

2. Review of Toxicological Review Document

Human Health and Ecotoxicological Effects of Concern -

- Adequacy of document in presenting and evaluating existing studies
- EPA analyses, biological significance of database, addressing inconsistencies
- Appropriate end points/time points and statistical analyses used by EPA authors?
- Any missing data/references that should be included?
- Sections that could be improved
- Is the document useful for purpose of characterizing risk to human health/ecotoxicological effects?

3. Hazard Characterization Human Health

- Are the NOAELs and/or LOAELs appropriately assigned for each study?
- Use of single study or totality of data on thyroid
- Were appropriate critical effect and LOAEL identified?
- Appropriateness of uncertainty factors of 3 for:
  - » interspecies extrapolation
  - » use of minimal LOAEL
  - » partially address intrahuman variability in PD
  - » database deficiencies
  - » intrahuman variation in iodide uptake inhibition.
- Are there data to support the position that the RfD will protect for both cancer and noncancer endpoints?

3. Hazard Characterization Ecotoxicological Assessment

- Have goals and objectives been adequately described and met?
- Does analysis support the conclusions? Uncertainties addressed?
- Can assays selected for evaluation be reasonably expected to identify potential ecological effects of concern?

4. Further Testing Needs Human Health

- Were the experimental designs of the studies adequate to identify the potential hormone disrupting effects on development and reproductive performance due to thyroid function perturbations at low exposure levels?
- Identify additional studies that would lead to a more complete toxicological characterization.
- Suggestions for protocols.
- Comment on the potential value added by the development of a PBPK model to address species differences in inhibition of iodide uptake, perchlorate kinetics, and subsequent perturbations of the hypothalamic-pituitary-thyroid axis.

4. Further Testing Needs Ecotoxicological

- Will the additional ecotoxicological studies currently underway be sufficient to characterize the ecotoxicological potential of perchlorate?
- If not, describe what more should be considered.

Panel Conclusions

Hazard Identification

- Hazards of perchlorate well delineated; it is not toxic to most organs and not mutagenic
- MOA is clear; toxic effects limited to inhibition of iodine uptake

Dose Response

- Thyroid cell hypertrophy is not an adverse effect, nor was it demonstrated to be correlated with an adverse effect
- Hyperplasia is potentially an adverse effect
- Dose response characterization for perchlorate is not robust because cannot distinguish dose response of hypertrophy from dose response of hyperplasia

Special Populations

- Since thyroid hormones are essential for normal development of the CNS, fetuses and neonates are the sensitive populations of concern

Risk Assessment

- Use of PBPK models appropriate and recommended
- Risk estimates based on human data should be more accurate than ones based on animal data
- Harmonization of cancer and noncancer risk assessment is commended
- Not possible to determine appropriate UF
- Proposed RfD is likely to be conservative

Panel Recommendations

- Convene a pathology working group
- Use uniform pathology grading criteria for all studies
- Establish dose-response curves for hypertrophy vs. hyperplasia and/or other adverse effects
- Evaluate effects on mental development during fetal and neonatal periods

- Determine transfer from mother to pup via milk
- Pursue a predictive risk assessment using PBPK modeling
- Conduct further studies on healthy human volunteers
- Provide a clear statement of strategy for using MOA and PBPK modeling in harmonization of cancer and noncancer

- Several specific recommendations regarding statistical analysis
- Conduct a predictive immunotoxicity test (e.g., sheep erythrocyte plaque assay) following both 14 and 90 days of exposure
- In future developmental studies, treat dams prior to conception to ensure they are hypothyroid during critical stages of fetal development

- In future developmental studies, correlate maternal and fetal serum hormone levels with thyroid histopathology, and fetal neurohistopathology
- Conduct a standard developmental toxicity study in rats, seemingly a more sensitive species
- Conduct further evaluation of pup thyroids at PND5 to determine significance of original findings

Post Peer Review Meeting

- Report on document and studies
- NCEA will generate responsiveness summary report
- NCEA will revise document